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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,432	10/15/2001	Chen-Kun James Shen	08919-016003	3256

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BOSTON, MA 02110

EXAMINER

KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action****Application No.**

09/977,432

**Applicant(s)**

SHEN, CHEN-KUN JAMES

**Examiner**

Sumesh Kaushal Ph.D.

**Art Unit**

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.
- b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_.

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 33-63.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☐ Other: \_\_\_\_\_

JEFFREY FREDMAN  
PRIMARY EXAMINER

10/26

Continuation of 5. does NOT place the application in condition for allowance because: Claims 33-36, 41-46, 51-53 and 58-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, ref of record) in view of Miller et al (Biotechniques 7(9):980-990, 1989 ref of record), for the same reasons of record as set forth in the office action mailed on 08/09/04.

Response to arguments

The applicant argues that Zhang vector, which functions in a non-viral vector, may not function in a viral vector and as a result one skilled in the art would not have been motivated to make viral vectors containing the  $\zeta$ -globin enhancer region. The applicant argues that to support this argument applicant cited McCune (a reference cited by applicant), who teaches that an enhancer that function well may not work in a viral vector. The applicant argues that McCune teaches, "finding may be applicable to the more general problem or sustaining expression of retrovirus-transduced genes. Based upon McCune teaching the applicant concluded that incorporation of  $\zeta$ -globin enhancer region in a viral vector is an unexpected combination.

However, this is found NOT persuasive because the response element as taught by McCune is not limited to the  $\zeta$ -globin enhancer (SEQ ID NO:1), therefore there is reasonable expectation of success that a response element other than as taught by McCune would function in any viral (retroviral) vector as claimed. Furthermore the scope of base claim 33 is not limited to a retroviral vector but encompasses other viral vectors. The office recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The applicant fails to consider the combined teaching of the reference cited herein in entirety.

Zhang teaches an expression vector comprising, a tissue specific  $\zeta$ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). Zhang further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif, gctgagtca to tctgagtca (SEQ ID NO:1,  $\zeta$ -globin enhancer) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (see Zhang page 8502, col.2 para.6; page 8504 fig-3, page 2304, fig-7). Miller teaches the making of a N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3). Therefore it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific  $\zeta$ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang and Jarman. In addition as one would have a reasonable expectation of success, since McCune does not specifically teach that the response element as claimed i.e. SEQ ID NO:1 would not work in a viral vector. In addition as discussed during the interview conducted on 05/27/04, various retroviral vectors encoding tissue specific enhancer elements were known in the art at the time of the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claims 37-40, 47-50, 54-57 and 60-63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, ref of record) in view of Miller et al (Biotechniques 7(9):980-990, 1989 ref of record ) as applied to claims 33-36, 41-46, 51-53 and 58-59 above, and further in view of Jarman et al (Mol. Cell. Bio. 11(9):4679-4689, 1991; ref of record), for the same reasons of record as set forth in the office action mailed on 08/09/04.

Response to arguments

The applicant argues that as pointed out above the cited art does not suggest a viral vector the contains  $\zeta$ -globin enhancer (SEQ ID NO:1), which is an unexpected result. The applicant concluded that incorporation of  $\zeta$ -globin enhancer region in a viral vector is an unexpected combination.

However, this is found NOT persuasive because the response element as taught by McCune is not limited to the  $\zeta$ -globin enhancer (SEQ ID NO:1), therefore there is reasonable expectation of success that a response element other than as taught by McCune would function in any viral (retroviral) vector as claimed. Furthermore the scope of base claim 33 is not limited to a retroviral vector but encompasses other viral vectors. Zhang teaches an expression vector comprising, a tissue specific  $\zeta$ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). Zhang further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif, gctgagtca to tctgagtca (SEQ ID NO:1,  $\zeta$ -globin enhancer) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (see Zhang page 8502, col.2 para.6; page 8504 fig-3, page 2304, fig-7). Miller teaches the making of a N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high-titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3). Therefore it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific  $\zeta$ -globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang and Jarman. In addition as one would have a reasonable expectation of success, since McCune does not specifically teach that the response element as claimed i.e. SEQ ID NO:1 would not work in a viral vector. In addition as discussed during the interview conducted on 05/27/04, various retroviral vectors encoding tissue specific enhancer elements were known in the art at the time of the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.